

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

REMARKS

Claims 11, 13-17, 21-23, 26 and 28-29 are in the application. Solely to advance prosecution, and without prejudice or disclaimer, Applicants herewith amend claim 11. Support for the amendment to claim 11 is found, *inter alia*, in claim 11 as originally presented. No new matter is added. Entry and consideration of Applicants' Amendment is therefore kindly requested.

I. Claims 11-17, 20-23, 26, 28 and 29 Are Enabled Under 35 U.S.C., § 112, First Paragraph

At page 4 of the Office Action, the Office rejects claims 11-17, 20-23, 26, 28 and 29 under 35 U.S.C., § 112, first paragraph as allegedly lacking enablement.

Solely to advance prosecution, and without prejudice or disclaimer, Applicants herewith amend the claims. Applicants' Amendment overcomes the rejection.

Withdrawal of the lack of enablement rejection is therefore kindly requested.

II. Claims 11-17, 20-23, 26, 28 and 29 Are Patentable Under 35 U.S.C. § 103

At page 6 of the Office Action, and at page 7, the Office rejects claims 11-17, 20-23, 26, 28 and 29 under 35 U.S.C. § 103 as allegedly being obvious over Lin et al. (U.S. Serial No. 4,831,192 A) and Lin et al. in view of Kudzma et al. (J. Med. Chem. 1989, 2534-42), respectively.

To establish *prima facie* case of obviousness all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Further, "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)). It is necessary

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ____ (2007). A *prima facie* case of obviousness may be rebutted by a showing of unexpectedly superior properties of the claimed invention compared to the closest prior art which is commensurate with the claims. *Kao Corp. v. Unilever United States Inc.*, 441 F.3d 963 (Fed. Cir. 2006). For unexpectedly superior properties, the comparison is made to the closest specifically disclosed composition/method of one piece of prior art, not with the combination of art used as the basis for the rejection. *In Re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Demonstration of unexpected superiority of a single property shared with the prior can rebut a *prima facie* case of obviousness. See, for example, *In re Papesch*, 315 F.2d 381 (CCPA 1963); *In re Lambooy*, 300 F.2d 950 (CCPA 1985); *In re Schechter*, 205 F.2d 185 (CCPA 1953); *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987); and *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007).

Applicants disagree with the Office that Applicants' claimed invention is rendered obvious by the references as cited by the Examiner. A corresponding compound of the formula (I'') wherein Z1 is ethylene whose representative example is Fentanyl is known to act on an opioid receptor with morphine, and to have analgesic activity. Lin et al. (i.e., '192) indicate a compound wherein Z¹ is ethylene. Lin et al. fail to teach or suggest neuromedin receptor function regulating activity. In synthetic processes, a benzyl group (Z1 = methylene) is widely used as a protective group of an amine and, in Kudzma *et al.*, compounds 8d-8k are synthesized as intermediates. Their biological activities are undisclosed and they do not have opioid activity. They are formed as mere intermediates. Nevertheless, Applicants teach the compound of formula (I'') wherein Z1 is methylene and the compound has neuromedin receptor function

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

regulating activity and is useful as a medicament. The Office is reminded that the law is clear that when the alleged prior art does not teach a specific or significant utility for the disclosed compounds, the art cannot render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less structurally related compounds. See MPEP § 2144.09 and *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971). In order to prove obviousness based on structural similarity between a claimed invention and the cited prior art, it is necessary to demonstrate that a reason or motivation to make the claimed compositions is indicated in the prior art reference. *In re Dillon*, 919 F.2d, 688 (Fed. Cir. 1990). No plausible reason or motivation is set forth.¹

It is also necessary to demonstrate that there exists adequate support in the cited reference for the necessary change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985). Nothing in the reference as cited by the Examiner refers to support for the necessary change in chemical structure or sets forth any suggestion or motivation to do so.

¹ The Office Guidelines, set forth in *Federal Register*, Vol. 72, No. 195, Wednesday, October 10, 2007, set forth plausible rationales, including combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; use of known technique to improve similar devices (methods, or products) in the same way; applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; “Obvious to try”—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. In maintaining the rejection, the Office fails to appreciate the unpredictability in the art of chemistry and drug development, which necessarily limits an overly broad application of KSR, which is inconsistent with the Guidelines and KSR.

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

In addition, the Office position contradicts the holding in *Eisai v. Dr. Reddy's and Teva Pharmaceuticals*, 533 F.3d 1353 (Fed. Cir. 2008), where the court held that a chemical compound was not obvious over the prior art, the court pointing out:

because "the record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property." "The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions." In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." [Emphasis Added]

The Examiner further fails to state a reason that would have prompted a person of ordinary skill in the art relevant field to obtain Applicants' claimed compound from the compound disclosed in the cited reference because the prior art indicates, "compounds of the present invention possess potent analgesic and anesthetic properties." Lin et al., column 1, lines 33-34. The Applicants discovered that the compound of the formula (I'') wherein Z1 is methylene has neuromedin receptor function regulating activity and is useful as a medicament. The Examiner's position is therefore inconsistent with precedent which indicates that a rationale must be set forth to support a charge of obviousness. *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ____ (2007). There is no articulated or logical rationale for compounds having analgesic and anesthetic properties rendering obvious Applicants' compounds directed to, for

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

example, hypertension, cardiac infarct or acute renal dysfunction. Therefore, it is clear that the corresponding compound disclosed in Lin et al. wherein Z1 is ethylene does not teach or suggest the compound of the present invention and therefore cannot possibly render obvious Applicants' invention.

Assuming arguendo a *prima facie* case of obviousness is set forth, which it is not, the attached Declaration of Mr. Tarui illustrates the unexpected properties of Applicants' claimed invention. Mr. Tarui compared the neuromedin U receptor antagonistic activities of Applicants' claimed compounds to compound 8f of Kudzma et al. (referred to as Test Compound A, at page 2 of Mr. Tarui's Declaration) which is the closest compound among the compounds indicated in the cited references (i.e., Lin et al. '192, Lin et al. '749 and Lin et al. '120 and Kudzma et al.) to the compound at issue in the rejection. This compound corresponds to the compound of Reference Example 38 described in Applicants' specification. Mr. Tarui found that the neuromedin U receptor antagonistic activities of Applicants' claimed compounds to compound 8f of Kudzma et al. were much higher than that of N-[1-benzyl-4-(4-methylthiazol-2-yl)-4-piperidinyl]-N-phenylpropionamide (Compound 8f of Kudzma et al.). The neuromedin U receptor binding inhibiting activities of the test compounds were determined according to Test Examples 1 to 4 of the present specification, and then compared. Page 9, Mr. Tarui's Declaration. As a result, the compound 8f (wherein R^{2b} is ethyl) exhibited a neuromedin U receptor binding inhibiting activity and had an IC₅₀ of 46nM. With regard to the neuromedin U receptor binding inhibiting activity, however, the compound wherein R^{2b} was methyl as described in claim 23 *had a higher activity* than the compound wherein R^{2b} was ethyl. Page 9, Mr. Tarui's Declaration. For example, the compound of Reference Example 39, which is the same as the compound 8f except that R^{2b} is changed to methyl, had an IC₅₀ of 24nM (see, Table

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

1 in the present specification). The compound of Reference Example 101 had an IC₅₀ of 22nM, the compound of Reference Example 80B had an IC₅₀ of 18nM, and the compound of Reference Example 83B had an IC₅₀ of 22nM. Page 9, Mr. Tarui's Declaration. Thus, it was found that the compound having R^{2b} of methyl smaller than ethyl had a higher activity. Such a structure-activity correlation was unexpected. Lin et al. '192, Lin et al. '749 and Lin et al. '120 and Kudzma et al. do not teach or suggest such an unexpected superior result of the present invention. Regarding *In re Wood*, 199 USPQ 137, cited at page 8 of the Office Action, the holding indicates, "we agree with appellants that an unexpected property possessed by a compound *would be evidence of its unobviousness.*" [Emphasis Added]. Furthermore, *In re May*, 574 F2d 1082 (1978) is pertinent, wherein the court held,

"In *In re Albrecht*, 514 F.2d 1389, 1395-96, 185 USPQ 585, 590 (CCPA 1975), the court stated: We are of the opinion that a novel chemical compound can be nonobvious to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound. [Emphasis in original and added.] Thus, merely because those skilled in the art would have expected the compound of claim 11 to have analgesic activity, does not mean, as the board apparently suggests, that an irrebuttable presumption of obviousness has been established. Those properties which would have been expected must be balanced against the unexpected properties."

[Emphasis Added].

In view of the above, reconsideration and withdrawal of the §103(a) rejection is respectfully requested.

AMENDMENT UNDER 37 C.F.R. § 1.116
U.S. Appln. No. 10/533,833 (Q101061)

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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